HFA-305
Documents Management Branch

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FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 140-865

Narasin (MONTEBAN®) plus Bacitracin zinc (BACIFERM®)

For the prevention of coccidiosis caused by *Eimeria necatrix, E. tenella, E. acervulina, E. brunetti, E. mivati* and *E. maxima*, and for increased rate of weight gain and improved feed efficiency in broiler chickens.

Sponsored by:

Roche Vitamins Inc.
45 Waterview Boulevard
Parsippany, New Jersey 07054

FOIS 1

FREEDOM OF INFORMATION SUMMARY

Combined use of MONTEBAN® and BACIFERM® in Broiler Chicken Feeds

I. GENERAL INFORMATION

NADA: 140-865

Sponsor: Roche Vitamins Inc.
45 Waterview Boulevard
Parsippany, New Jersey 07054

Generic Names: Narasin
Bacitracin zinc

Trade Names: MONTEBAN®
BACIFERM®

Marketing Status: OTC

II. INDICATIONS FOR USE

For the prevention of coccidiosis caused by *Eimeria necatrix, E. tenella, E. acervulina, E. brunetti, E. mivati,* and *E. maxima.* For increased rate of weight gain and improved feed efficiency in broiler chickens.

III. DOSAGE

A. Dosage form: This NADA provides for the combined use of these two Type A medicated articles: narasin as per 21 CFR 558.363, and bacitracin zinc as per 21 CFR 558.78. Narasin is supplied as a Type A medicated article in concentrations of 36, 45, 54, 72, or 90 grams narasin activity per pound. Bacitracin zinc is supplied as a Type A medicated article in a single concentration of 10, 25, 40, or 50 grams of bacitracin zinc activity per pound.

B. Route of Administration: Oral, via the feed.

C. Recommended Dosage:

Narasin	Narasin is added to broiler chicken feed at concentrations from 54 to 72 g/ton for the prevention of coccidiosis caused by *Eimeria necatrix, E. tenella, E. acervulina, E. brunetti, E. mivati,* and *E. maxima.*

Bacitracin zinc	Bacitracin zinc is added to broiler chicken feed at concentrations from 4 to 50 g/ton for increased rate of weight gain and improved feed efficiency.

IV. EFFECTIVENESS

In accordance with the Federal Food, Drug, and Cosmetic Act (FFDCA), as amended by the Animal Drug Availability Act of 1996, if the active ingredients or animal drugs intended for use in combination in animal feed have previously been separately approved for the particular uses and conditions of use for which they are intended for use in combination, FDA will not refuse to approve an NADA for the combination on effectiveness grounds unless the Agency finds that the NADA fails to demonstrate that: 1) there is substantial evidence to demonstrate that any active ingredient or animal drug intended only for the same use as another active ingredient or animal drug in the combination makes a contribution to the labeled effectiveness, 2) each of the active ingredients or animal drugs intended for at least one use that is different from all other active ingredients or animal drugs used in the combination provides appropriate concurrent use for the intended target population, or 3) where the combination contains more than one nontopical antibacterial active ingredient or animal drug, there is substantial evidence that each of the nontopical antibacterial active ingredients or animal drugs makes a contribution to the labeled effectiveness (21 USC §512 (d)(4)(D)).

Narasin, as provided by Elanco Animal Health, has previously been separately approved for use in broiler chicken feeds for the prevention of coccidiosis caused by *Eimeria necatrix, E. tenella, E. acervulina, E. brunetti, E. mivati,* and *E. maxima* (21 CFR 558.363(d)(1)). Bacitracin zinc, as provided by Roche Vitamins Inc., has previously been separately approved for use in broiler chicken feeds for increased rate of weight gain and improved feed efficiency (21 CFR 558.78(d)(1)(i)). Effectiveness for each drug, narasin and bacitracin zinc, when administered alone in accordance with its approved uses and conditions of use, is demonstrated in Elanco Animal Health's approved NADA 118-980 to which Roche Vitamins Inc. has right of reference, and in Roche Vitamin Inc.'s previously approved NADA 46-920. Because narasin and bacitracin zinc each have at least one use that is different from all other animal drugs used in the combination, the NADA must also demonstrate that narasin plus bacitracin zinc provide appropriate concurrent use for the intended target population. The use of narasin plus bacitracin zinc provides appropriate concurrent use because these drugs are intended to treat different conditions (narasin, coccidiosis; bacitracin zinc, performance) likely to occur simultaneously with sufficient frequency in broiler chickens. There is no more than one nontopical antibacterial (bacitracin zinc) contained in this combination animal drug intended for use in Type C medicated feed. Narasin is not considered to be an antibacterial animal drug for use in broiler chickens for the purposes of §512 (d)(4) of the FFDCA, because narasin is approved only for prevention of a protozoal disease in broiler chickens.

V. ANIMAL SAFETY

In accordance with the FFDCA, as amended by the Animal Drug Availability Act of 1996, if the active ingredients have previously been separately approved for the particular uses and conditions of use for which they are intended for use in combination, FDA will not refuse to approve an NADA for the combination on target animal safety grounds unless there is a substantiated scientific issue specific to an active ingredient or animal drug used in the combination or a scientific issue is raised by target animal observations contained in studies submitted to the NADA for the combination and FDA finds that the application fails to establish that such combination active ingredient or animal drug is safe for the target animal.

Narasin, as provided by Elanco Animal Health, has previously been separately approved for use in broiler chicken feeds for the prevention of coccidiosis caused by *Eimeria necatrix, E. tenella, E. acervulina, E. brunetti, E. mivati,* and *E. maxima* (21 CFR 558.363(d)(1)). Bacitracin zinc, as provided by Roche Vitamins Inc., has previously been separately approved for use in broiler chicken feeds for increased rate of weight gain and improved feed efficiency (21 CFR 558.78(d)(1)(i)). Target animal safety for each drug, narasin and bacitracin zinc, when administered alone in accordance with its approved uses and conditions of use, is demonstrated in Elanco Animal Health's approved NADA 118-980, to which Roche Vitamins Inc. has a right of reference and in Roche Vitamins Inc.'s approved NADA 46-920. The Agency has found no substantiated scientific issue relating to the target animal safety of narasin or bacitracin zinc when used in combination under this NADA and no scientific issue has been raised by target animal observations submitted as part of the NADA for this combination. Thus, pursuant to FFDCA, as amended by the Animal Drug Availability Act of 1996, no specific target animal safety study (ies) is (are) required for approval of NADA 140-865.

VI. HUMAN SAFETY

In accordance with the FFDCA, as amended by the Animal Drug Availability Act of 1996, if the active ingredients or animal drugs intended for use in combination have previously been separately approved for the particular uses and conditions of use for which they are intended for use in combination, FDA will not refuse to approve an NADA for the combination on human safety grounds unless one or more of the active ingredients or animal drugs used in the combination at the longest withdrawal for the respective active ingredients or animal drugs in the combination exceeds the established tolerance, or one or more active ingredients or animal drugs in the combination interferes with the method of analysis for another active ingredient or drug in the combination.

A. Toxicity Studies

Safety of this combination product has been established by data in NADA 46-920 for bacitracin zinc and in NADA 118-980 for narasin.

B. Tolerances

The tolerance for bacitracin zinc in the uncooked edible tissues of chickens is of 0.5 ppm (0.02 unit per gram), negligible residue (21 CFR 556.70). Elanco Animal Health has submitted a supplement to the parent narasin NADA (NADA 118-980) that will amend 21 CFR 556.428. The amended section will include a tolerance in the abdominal fat of chickens of 480 ppb.

C. Residue Non-Interference Study

Residue data supporting the approved individual uses of bacitracin zinc and narasin, each having zero withdrawal times, were submitted in their respective original applications (see Part A, above). A tissue residue study (Study No. PLR-950) was conducted to demonstrate that there is no change in the residue depletion pattern for the combination product, bacitracin zinc and narasin, when fed to broiler chickens and that the presence of the drugs in the same chicken tissue did not interfere with the assay of either drug. The in-life portion of the study and bacitracin zinc assays were conducted at Pitman-Moore Inc., Terre Haute, Indiana. Narasin assays were performed at Lilly Research Laboratories, Greenfield, Indiana.

Fifteen female and male broiler chickens were medicated with bacitracin zinc (100 g/ton), roxarsone (45 g/ton), and narasin (72.5 g/ton) for 41 days until slaughter at 6 hours (practical zero), or 1, 2, 3, or 5 days following medicated feed withdrawal.

Mean Bacitracin Zinc Residues in Muscle and Mean Narasin Residues in Fat Collected from Chickens Treated with Medicated Feed Containing 100 g/ton Bacitracin Zinc, 45 g/ton Roxarsone, and 72.5 g/ton Narasin for 41 Days

	Day 0	Day 2	Day 3	Day 5
Bacitracin Zinc	<LOQ of 0.24 ppm	not assayed	not assayed	not assayed
Narasin	0.051 ppm	<LOQ of 0.01 ppm	<LOQ of 0.01 ppm	<LOQ of 0.01 ppm

The assay was validated by analyzing tissue samples spiked with narasin and bacitracin zinc. Control muscle samples fortified with narasin (200 ppb) and bacitracin zinc (0.5 ppm) demonstrated that no interference was observed with the assay of bacitracin zinc in the presence of narasin. Control fat samples fortified with 200 ppb bacitracin zinc and 20 ppb narasin demonstrated that no interference was observed with the assay of narasin in the presence of bacitracin zinc.

Residues for bacitracin zinc and narasin were below their respective tolerances at zero withdrawal, the established withdrawal periods for each of the drugs, thereby indicating an absence of interference.

D. Regulatory Methods

The regulatory analytical method for detection of residues of bacitracin zinc is a microbiological test using Micrococcus luteus (ATCC 10240) suspension. The method is published by the Food and Drug Administration, "Antibiotic Residues in Milk, Dairy Products and Animal Tissues: Method, Reports, and Protocols, revised October 1968, reprinted December, 1974". A method capable of determining parent narasin in abdominal fat is on file with the Center for Veterinary Medicine. Both methods are available from the Center for Veterinary Medicine, 7500 Standish Place, Rockville, MD 20855.

The data demonstrate that residues of narasin and bacitracin zinc are below their respective tolerances at zero withdrawal, the established withdrawal period for each drugs, thereby indicating an absence of interference.

VII. AGENCY CONCLUSIONS

The data submitted in support of this NADA comply with the requirements of §512 of the FFDCA and demonstrate that narasin (54 to 72 g/ton) plus bacitracin zinc (4 to 50 g/ton) are safe and effective for the claims indicated in Section II of this FOI summary.

Pursuant to 21 CFR 514.106 (b)(2)(vi), this combination NADA approval is regarded as a Category II supplemental change which did not require a reevaluation of safety and efficacy data in the parent NADAs. The drugs are to be fed in Type C medicated feeds, in accordance with Section II and III of the FOI Summary and the Blue Bird labeling that is attached to this document.

Attached labeling: Type C medicated feed (Blue Bird).

Net weight lb (kg) on bag or bulk

Narasin/Bacitracin Zinc Broiler Chicken Ration

Type C Medicated Feed

For the prevention of coccidiosis caused by *Eimeria necatrix, E. tenella, E. acervulina, E. brunetti, E. mivati,* and *E. maxima*, and for increased rate of weight gain and improved feed efficiency in broiler chickens.

ACTIVE DRUG INGREDIENT

Narasin..... 54 to 72 g/ton
Bacitracin zinc..... 4 to 50g/ton

GUARANTEED ANALYSIS

Crude Protein, not less than..... _____%
Lysine, not less than..... _____%
Methionine, not less than..... _____%
Crude Fat, not less than..... _____%
Crude Fiber, not more than..... _____%
Calcium, not less than..... _____%
Calcium, not more than..... _____%
Phosphorus, not less than..... _____%
Salt[1], not less than..... _____%
Salt[1], not more than..... _____%
Sodium[2], not less than..... _____%
Sodium[2], not more than..... _____%

[1]If added.
[2]Shall be guaranteed only when total sodium exceeds that furnished by the maximum salt guarantee.

INGREDIENTS

Each ingredient must be named in accordance with the names and definitions adopted by the Association of American Feed Control Officials.

DIRECTIONS FOR USE

Feed continuously as the sole ration.

CAUTION: Do not allow adult turkeys, horses or other equines access to formulations containing narasin. Ingestion of narasin by these species has been fatal.

MANUFACTURED BY

BLUE BIRD FEED MILL
Anytown, USA 12345